UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,843	02/09/2004	Tony Peled	24024-505	9770

30623 7590 03/30/2009

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
03/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,843	PELED ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *401,411,412,414,416-419,422-424,437,438,462,464-467 and 469-481* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401,411,412,414,416-419,422-424,437,438,462,464-467 and 469-481* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-05-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Toni Peled filed on 12-30-2008.
3. Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462, 464-467 and 469-481 are pending. Claims 401, 411, 412, 416, 419, 462, 465 have been amended and claims 469-481 have been added by Applicants' amendment filed on 12-30-2008.
4. Therefore, claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462, 464-467 and 469-481 are currently under examination to which the following grounds of rejection are applicable.

Priority

This application which claims the benefit under 35 U.S.C. 119(e) of prior-filed provisional application 60/404,137, filing date 08/19/2002, and 60/376,183, filing date 04/30/2002, is acknowledged.

Review of the priority documents provides no literal or figurative support for the claimed invention of "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide". Therefore, the priority date for the claimed limitation "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide' is found in the disclosure of the instant U.S. Application filed on 02-09-2004.

Withdrawn Rejections in response to Applicants' arguments or amendments.

Claim Rejections - 35 USC § 103

In view of Applicants' amendment of claims 401, 411, 42, 462 to recite "the presence of 1.0 mM to 10 mM of exogenously added nicotinamide" rejection of claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462, 464, and 466-467 under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) has been withdrawn.

Though Brown teaches the requirements for the basal medium composition for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (i.e. 0.033mM) or theoretically up to 10 times as much, Brown does not teach or suggest concentrations of 1.0 mM to 10 mM of nicotinamide capable of supporting expansion while substantially inhibiting differentiation of hematopoietic CD34+/CD38 cells.

Claim Rejections - 35 USC § 102(b)

In view of Applicants' amendment of claim 411 to recite "the presence of 1.0 mM to 10 mM of exogenously added nicotinamide" rejection of claim 411 under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999) has been withdrawn.

Though Brown teaches a transplantable hematopoietic cell preparation comprising an expanded population of CD34+ hematopoietic stem cells propagated *ex vivo* in the presence of a basal medium composition for expansion of CD34+/CD38- cells including nicotinamide at concentration of 4 mg/L (i.e. 0.033mM) or theoretically up to 10 times as much, Brown does not

teach or suggest concentrations of 1.0 mM to 10 mM of nicotinamide capable of supporting expansion while substantially inhibiting differentiation of hematopoietic stem cells.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim objections

In view of Applicants' amendment of claim 416, objection to claim 416 because a grammatical error, has been withdrawn.

Claim Rejections - 35 USC § 102(b)

In view of Applicants' amendment of claims 401, 411, 42, 462 to recite "the presence of 1.0 mM to 10 mM of exogenously added nicotinamide", rejection of claims 401, 412, 414, 416-419, 422-424, 464 and 466 under 435 U.S.C. 102(b) as being anticipated Brown et al., (US Patent Number 5,945,337, Date of Patent Aug. 31, 1999) has been withdrawn.

The instant claims, drawn to methods of expanding a CD34+ hematopoietic stem cells *ex-vivo,* specifically require exogenously added concentrations of nicotinamide of 1.0 mM to 10 mM to CD34+ cell cultures.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment claims 419 and 465 to refer to the proper corresponding antecedent, rejection of claims 419 and 465 under 35 U.S.C. 112, second paragraph as being indefinite for lacking proper antecedent bases has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Claim Rejections - 35 USC § 103

In view of Applicants' amendment of claim 401 to recite "the presence of 1.0 mM to 10 mM of exogenously added nicotinamide" rejection of claims 401, 437 and 438 under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) in view of Banasik et al., (1992, JBC, pp. 1569-1575, of record) has been withdrawn.

Though Brown teaches a transplantable hematopoietic cell preparation comprising an expanded population of CD34+ hematopoietic stem cells propagated *ex vivo* in the presence of a basal medium composition for expansion of CD34+/CD38- cells including nicotinamide at concentration of 4 mg/L (i.e. 0.033mM) or theoretically up to 10 times as much, Brown does not teach or suggest concentrations of 1.0 mM to 10 mM of nicotinamide capable of supporting expansion while substantially inhibiting differentiation of hematopoietic stem cells.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

New Grounds of Rejection necessitated by Applicants' amendment of the claims in the response filed on 2/05/2009

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 401, 411, 412, 414, 416-419, 422-424, 462, 464-467 and 469-481 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002). **This is a new rejection necessitated by amendment of the claims in the response filed 12-30-2008.**

Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from umbilical cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]). Moreover, Brown R. discusses that one or more of the cytokines playing a role for driving proliferation in hematopoietic cells can be added to the culture medium at different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]). Note that G-CSF is a late acting cytokine. Also note that the

instant claims do not place any limitations as to the particular combination of cytokines selected or concentrations used. Moreover, Brown R teaches the components of the basal medium for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (p. 3, col. 2, [0040] and p. 4, table I) (4 mg/L is equivalent to 0.033mM). Brown discloses that Iscove's modified Dulbecco's medium (IMDM) can reformulated and "it is expected that the reformulation will contain those essential components of IMDM in amounts 0.1 to 10, preferably 0.5 to 2 times, most preferably 0.8 to 1.2 times their amounts" (p. 4, [0045]). Though Brown et al., does not specifically disclose that expansion of CD4+ substantially inhibits differentiation, substantial inhibition of differentiation is necessarily present as the culturing conditions in Brown are the same. Note that claims 412 and 462 do not recite the limitation, "substantially inhibiting differentiation of the stem cells *ex-vivo*". **(Current claims 401, 412, 414, 416, 418, 422-424).** Additionally, Brown discloses that umbilical cord blood as the source of HSCs contains a reduced number of stem cells compared to bone marrow as determined by enumeration of nucleated mononuclear cells and/or CD34+, indicating the presence of a mixed cell population (p. 1, [0008]), (**Current claim 417**). Furthermore, Brown discloses that "Early progenitors (CD34, CD38, HLA-DR), myeloid markers (CD33, CD14, CD45), lymphocyte markers (CD3, CD7, CDI9), red blood cell markers (glycophorin A) and megakaryocyte/platelet determinants (CD41a)" and assesses by FACS the cluster of markers CD45, CD14, CD34, CD20, CD33, CD3, CD7, CD56, CDIO, CD4, CD8 (BDIS) and glycophorin A (p. 8, [0102]), Thus Brown does not explicitly discloses diminished expression of CD33, CD14, CD3 and other surface makers, reduction of said markers is inherently anticipated in an expanded population of CD34+ cells as CD33, CD14, CD3 makers identify differentiated stem cell populations

(Current claim 419). Furthermore, Brown R. exemplifies cultures of the bone marrow CD34+ enriched population showing CD34+/CD38- cells with significant expansion at day 3, 7 and 14, in the absence of serum and low concentrations of IL-3, IL-6 and SCF (p. 10, [0119]) reading on expansion of cells for a period of up to three weeks **(Current claims 419, 464, 465, 466)**

Brown does not specifically teach concentrations of exogenously added nicotinamide of 1.0 mM to 10 mM.

However, at the time the invention was made, Block discloses a chemically defined mammalian cell culture medium that supports maintenance and long term clonal growth of mammalian hepatocytes and other cells (col. 1, lines 10-15, col. 2, lines 1-3; col. 7, lines 1-5). At table II, (col. 10, lines 30-50), Block teaches various growth factors that can be added to the stock basal media to induce accelerated growth (col. 11, lines 28-38) including concentrations of nicotinamide in the range of 1-3050 mg/L, preferably 610.0 mg/L (610-3050 mg/L is equivalent to 5 to 25 mM of nicotinamide). Furthermore, Block teaches that after 14 days of growth, removal of nicotinamide from media components has the most dramatic effect in reducing cell proliferation, only second to removal of dexamethasone (col. 14, lines 11-26) (see Table IV for effect of removal of nicotinamide in reduction of cell growth). Moreover, Block teaches that proliferation of hepatocytes, in part, results from facultative stem cell growth (col. 1, lines 60-66, bridging to col. 2, lines 1-5) (Current claims 411, 462, 468-480). It is noted that Block describes that expansion of cells may occur without exogenously adding nicotinamide, for example, by addition to the stock basal media of at least one supplemental component such as Dexamethasone **(Current claim 481)**

Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, to increase the concentration of exogenously added nicotinamide to the culture media taught by Brown R. in an attempt to provide an improved formulation of the IMDM for preferential *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- hematopoietic stem cells, particularly because Block clearly discloses, in an unequivocal manner, that exposing a mixed population of hepatocytes including stem cells to nicotinamide at concentrations of 0-3050 mg/L, and preferentially 610.0 mg/L (e.g., equivalent to 5 mM), sustained long term proliferation and viability of hepatocytes. The manipulation of previously identified media components to determine cell growth and proliferation in a culture plate is within the ordinary level of skill in the art of cell and tissue culture. Because both Brown and Block teach media comprising nicotinamide for expansion of stem cells, it would have been obvious to increase exogenously added nicotinamide in the IMDM of Brown to 1.0 mM to 10 mM to achieve the predictable result of *ex vivo* expansion of hematopoietic stem cells and substantial inhibition of differentiation of the same cell population given the results of Brown and Block demonstrating the success of the methodology and materials detailed in each of the disclosures.

Response to Applicants' Arguments as they apply to rejection of claim 401, 411, 412, 414, 416-419, 422-424, 462, 464-467 and 469-481 under 35 USC § 103

At page 9 of Remarks, Applicants argue that as "As shown in the attached Peled Declaration, nicotinamide concentrations of up to 10 times the 4 mg/L nicotinamide disclosed by Brown are ineffective for *ex-vivo* expansion and inhibition of hematopoietic stem/progenitor cells, as compared with cells cultured in the presence of cytokines and nutrients alone (0.0 mM

nicotinamide). See, Peled Declaration at pages 2-4 and at Figure 1. As such, Brown teaches away from claimed the invention by suggesting that nicotinamide is not useful for ex-vivo expansion and inhibition of differentiation of hematopoietic stem cells".

At the outset, the examiner notes that claim 401 and new claim 481 recite, "a method for expanding a population of CD34+ hematopoietic stem cells *ex-vivo*, while at the same time, substantially inhibiting differentiation", claim 412 recites "expanding a population of CD34+ hematopoietic stem cells while inhibiting differentiation of said CD34+" and claim 462 recites, "culturing … *ex vivo* under conditions that result in proliferation of CD34+cells". Thus it is unclear to what extent CD34+cells differentiation is "substantially" inhibited. Hence, inhibiting 2 or 3 CD34+cells from differentiating would read on the breadth of the instant invention as the structural limitation of the methods claimed is obviated by the combined disclosures of Brown and Block. As set forth in the paragraph above, Brown and Block teach media components for ex *vivo* expansion (e.g. proliferation) of CD34+/CD38- and hepatocyte or "oval cells" that mature in hepatocytes, respectively. In an attempt to provide an improved formulation of the IMDM for preferential *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- , it would have been obvious to optimize the concentration of nicotinamide to a preferred concentration of 610.0 mg/L (e.g., equivalent to 5 mM), particularly because Block evidences that at this concentration, nicotinamide is critical in maintaining long term proliferation of facultative stem cells that differentiate into hepatocytes. It is noted that in the Peled Declaration at page 4, Table 1, Figure 1, nicotinamide appears to be critical for expansion of CD34+CD38- in the range of 2.5 to 5 mM after one week period, which is supported by the disclosure of Fig. 15 in the specifications. In

contrast, nicotinamide at concentration of 1 mM does not appear to have a significant effect on CD34+CD38- expansion after 3 weeks (see Specification, figure 15).

Claims 437 and 438 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002) as applied to claims 401, 411, 412, 414, 416-419, 422-424, 462, 464-467 and 469-481 above, and further in view of Banasik et al., (1992, JBC, pp. 1569-1575, of record). **This is a new rejection necessitated by amendment of the claims in the response filed 12-30-2008.**

The teachings of Brown and Block are outlined in the paragraph above. The combined disclosure fails to teach benzamide as the nicotinamide analog.

However, at the time the invention was made, Banasik et al., discloses specific inhibitors of ADP-ribosyltransferases, specially poly(ADP-ribose). Banasik et al., illustrates in Table 1, at page 1573, the comparative effect of various compounds on inhibition of poly(ADP-ribose) synthetase activity including nicotinamide (number 27), benzamide as a potent inhibitor and numerous benzamide analogs (Banasik et al., JBC, p. 1570, col. 1, paragraph 2; Table 1, numbers 22, 45, 103, 113, 77 and others).

Thus, it would had been *prima facie* obvious for the skilled artisan to substitute nicotinamide by any benzamide or benzamide analog because the function of both compounds were well known in the art as inhibitors of poly(ADP-ribose) synthetase activity. One of ordinary skill in the art could have substituted one known element for another and the result of the

substitution would have been predictable. Thus the combination of Brown, Block and Banasik et al., obviate the instant invention.

Response to Applicants' Arguments as they apply to rejection of claim 437 and 438 under 35 USC § 103

At pages 10 and 11 of Remarks, Applicants allege that "Banasik does not cure the deficiencies of Brown. By contrast, Banasik merely discloses that benzamide, as well as nicotinamide, is an inhibitor of poly(ADP-ribose) synthetase activity. Banasik is silent with regard to the use of nicotinamide or nicotinamide analogs for expansion and inhibition of differentiation of hematopoietic stem cells". Such is not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner refers applicants to the reasons set forth in the paragraphs above in relation to the obviousness to replace nicotinamide with benzamide, which is a nicotinamide analog.

Conclusion

Claims 401, 411, 412, 414, 416-419, 422-424, 437, 438, 462, 464-467 and 469-481 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is

(866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633